JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

ADVANCES IN ANALYTICAL AND BIOANALYTICAL METHODS FOR CELECOXIB DETERMINATION: A REVIEW

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ABSTRACT:
Celecoxib is a selective COX-2 inhibitor. The way non-steroidal anti-inflammatory drugs (NSAIDs) function is by blocking the COX enzyme, which is an inflammatory mediator. Osteoarthritis, rheumatoid arthritis, and primary dysmenorrhea are all treated with celecoxib. Therefore, the main objective of this work is to examine celecoxib in pharmaceutical and biological formulations using both qualitative and quantitative methods. In this review paper, we have compiled the methodologies for estimating celecoxib based on liquid chromatography- mass spectroscopy (LC-MS), high-performance liquid chromatography (HPLC), and UV/Vis spectroscopy. Furthermore, we have discussed the bioanalytical methods for CXB analysis. To sum up, this review article will assist researchers in developing new methods for estimating drug concentrations in biological fluids and pharmaceutical dose forms.

KEYWORDS: Celecoxib, Analytical method, High-performance liquid chromatography, liquid chromatography-mass spectroscopy, Bioanalytical methods.

INTODUCTION:
Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat the pain and inflammation associated with rheumatoid arthritis. Their chemopreventive effects and analgesic and anti-inflammatory qualities stem from their inhibition of cyclooxygenase (COX) enzymes, which change arachidonic acid into prostaglandins.(1) A highly specific inhibitor of cyclooxygenase–2 (COX–2) is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1- yl]benzenesulfonamide.(1) Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are the two kinds of the enzyme. Normal physiological prostaglandin-mediated processes like platelet aggregation and stomach cytoprotection are regulated by COX-1. The suppression of COX-1 by nonselective NSAIDs has been linked to stomach damage and platelet inhibition. It is commonly recognized that COX-2 plays a major role in the production of prostanoid mediators of pain and inflammation.(2) Clinical research has shown that celecoxib effectively reduces edema, discomfort, and sensitivity in the joints while also lowering the risk of stomach ulcers. Furthermore, new research has shown that COX-2 inhibitors reduce the growth of colon polyps.(2)

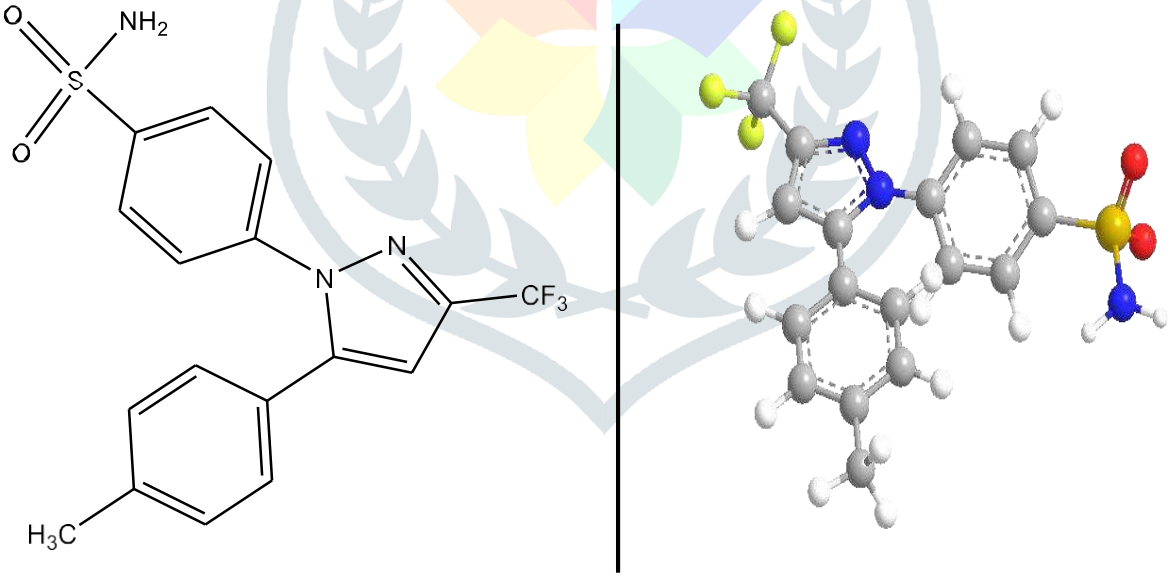

Figure 1: Chemical Structure of Celecoxib Mechanism of Action :

Celecoxib is a selective non-competitive inhibitor of cyclooxygenase-2 (COX-2) enzyme, in contrast to other NSAIDs, which inhibit both forms of cyclooxygenases (COX-1 and COX-2). In tissues that are inflammatory, COX-2 is highly expressed due to the induction of inflammatory mediators. Prostaglandin E2 (PGE2), prostacyclin (PGI2), thromboxane (TXA2), prostaglandin D2 (PGD2), and prostaglandin F2 (PGF2) are among the metabolites whose synthesis is decreased when this enzyme is inhibited. Pain and inflammation are reduced as a result of the suppression of these mediators. Non-steroidal anti-inflammatory medicines (NSAIDs) damage mucosa, induce ulceration, and worsen ulcer complications throughout the gastrointestinal tract by preventing prostaglandin formation. Compared to placebo, celecoxib has a lower

effect on the creation of prostaglandins in the stomach mucosa, which reduces the risk of ulceration.

Pharmacokinetics:

Absorption:

Celecoxib enters the gastrointestinal system quickly.7. Within three hours, the peak plasma levels of celecoxib were reached in healthy research individuals who received a single oral dose of 200 mg. 705 ng/mL is the Cmax. On or before day 5, steady-state concentrations are obtained when numerous doses are administered. Peak plasma levels are delayed by one to two hours when taken with a high-fat meal, and total absorption (AUC) increases by 10% to 20%. Patients with chronic renal impairment have been demonstrated to have a considerably decreased AUC for celecoxib. For unclear reasons, a meta-analysis of pharmacokinetic studies revealed that black patients' celecoxib AUC (area under the curve) was about 40% higher than that of Caucasians.[3]

Protein binding: 97%[3]

Metabolism: Cytochrome P450 2C9 plays a major role in the liver's metabolism of celecoxib, with minor assistance from CYP3A4, CYP2C8, and potentially even CYP2D6. It is biotransformed into metabolites of glucuronides and carboxylic acids. Three metabolites have been identified in human plasma following celecoxib administration: a main alcohol, a carboxylic acid, and a glucuronide conjugate. In terms of COX enzyme inhibition, these are regarded as inactive metabolites. Celecoxib should be provided cautiously to patients who, based on their past medical history, are known or suspected to have impaired cytochrome P450 2C9 activity or function. This is because these patients may have unusually high serum concentrations of celecoxib due to poor metabolism.[3]

Pharmacodynamics: By blocking the cyclooxygenase 2 (COX-2) enzyme, celecoxib lowers inflammation and pain. Even though the risk of bleeding with celecoxib is lower than with certain other NSAIDS, it still remains, thus care must be taken when giving it to people who have a high risk of gastrointestinal bleeding.[3]

Analytical Account of CXB

An extensive literature search revealed a variety of analytical methods, including UV/Visible Spectrophotometry, HPLC, HPTLC, UPLC, LC-MS/MS, and bioanalytical approaches, for the determination of RFX in bulk and pharmaceutical formulations. Etoricoxib (ETX), Valdecoxib (VDX), Salicylic acid (SCA), Amlodipine (AMD), Dezocine (DEZ), Dexmedetomidine (DEX), Ketoprofen (KPF), Nimesulide (NMS), Repaglinide (REP), Rofecoxib (RFX), Docetaxel (DTX), Ibuprofen (IBU), Diclofenac (DIC), are all evaluated alone as well as in conjunction with CXB **Figure 2** shows different analytical methods implemented for the estimation of CXB.

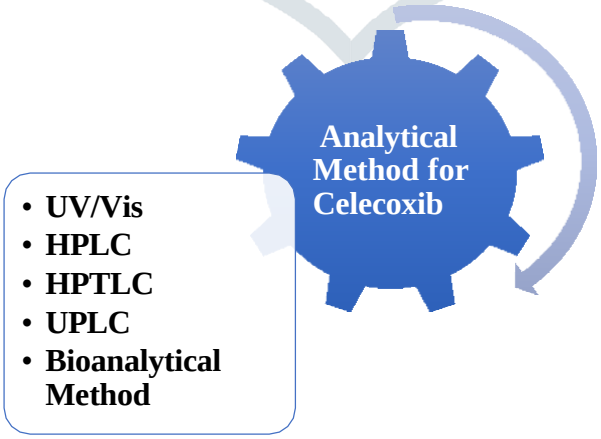

Figure 2: Analytical methods of Celecoxib

Bio-analytical method for CXB

A branch of analytical chemistry known as "bio-analysis" deals with the quantitative measurement of biotics (macromolecules, proteins, DNA, large-molecule drugs, metabolites) and xenobiotics (drugs and their metabolites) in biological systems. The summary of the reported bioanalytical methods is shown in **Table 1**

Table 1: Bioanalytical determination of CXB

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref
1	CXB	Human plasma	HPLC	va Pak C8 column	215 nm	SC-236	1
2	CXB	Human plasma	HPLC	Zorbax Eclipse Extend C18 column	***	Dimethyl - Celecoxib	2
3	CXB	Human plasma and breast milk	HPLC	C18 column	254 nm	***	4
4	CXB	Human plasma	HPLC	Monolithic silica column	254 nm	Mefenamic acid	5
5	CXB	Human plasma	HPLC	cleosil CN column	260 nm	Flutamide	6
6	CXB	Rat plasma	HPLC	C18 analytical column	254 nm	Ibuprofen	7
7	CXB	Rat plasma	HPLC	C18 reverse phase column	254 nm	Ketoprofen	8
8	CXB	Human plasma	HPLC	C18 µ-Bondapak HPLC column	260 nm	Flutamide	9
9	CXB	Human plasma	HPLC	Nucleosil- NO column	260 nm	***	10
10	CXB	Human serum	HPLC	Prontosil C AQ column	240 nm	methylated analogue	11
11	CXB	Human serum	HPLC	8 Wakosil column	250 nm	Tolbutamide	12
12	CXB	Human plasma	HPLC	hauer C18 column	250 nm	***	13
13	CXB	Skin samples	HPLC	C18 column	251 nm	Caffeine	14
14	CBX	Human urine	HPLC	Spherigel C18 column	255 nm	***	15

15	CXB	Human plasma	HPLC	Nucleosil C8 guard column	260 nm	Rofecoxib	16
16	REP, CXB	Male Sprague-Dawley rats	HPLC	Reversed C18 column	240 nm	Ketoconazole	17
17	RFX, CXB	Human plasma	HPLC	Zorbax SB- CN analytical column	254 nm	4-*n*-pentyl-phenyl-acetic acid	18
18	DTX, CXB	Rat plasma	HPLC	Reversed-phase C18 µ-Bondapack column	230 nm	Paclitaxel	19
19	IBU, DIC, CXB	Human urine	HPLC	MZ ODS-C18 column	330 nm	***	20
20	DIC, RFX, NIF, CXB	Human serum	HPLC	C18 bonded silica column	261 nm, 288 nm, 282 nm, 254 nm	***	21
21	CXB, OH- CXB, COOH-CXB	Human plasma	HPLC	C18 reverse phase column	254 nm	Phenacetin	22
22	ETX, SCA, VDX, KPF, NMS, CXB	Human plasma	HPLC	Kromasil KR 100-5C18 column	235 nm	DRF-4367	23
23	CXB	Human plasma	LC-MS	Shim Pack GLC-CN, C column	***	Sulindac	24
24	CXB	Rat blood	UPLC- MS/MS	henomenex Aqua C18	254nm	1-(4-sulfamoylphenyl)-5-(*p*-tolyl)-1*H*-pyrazole-3-carboxylic acid	25
25	CXB	Rat and human liver microsomes	UPLC- MS/MS	UPLC BEH C18 column	***	Carbamazepine	26

26	ETX, CXB	Serum and synovial fluid of inflammatory arthritis patients	UPLC/ICPMS	uity C18 BEH	***	***	27
27	CBX, DEZ, DEX	Beagle plasma	UPLC- MS/MS	UPLC BEH C18 coumn	***	Midazolam	28

*** Not Provided

UV-Visible spectroscopy method for CXB

The spectrophotometric methods have been accounted for the determination of CXB. The details of Spectrophotometry determination of basic principle, sample matrix, lambda max, solvent linearity range and the correlation coefficient are summarized in **Table 2.**

Table 2: Spectrophotometric methods used for determination of CXB

Sr. No.	**Drug**	**Matrix**	**Solvent**	**ambda Max** (nm)	**Linearity** (µg/mL)	**Correlation coefficient** (R2)	**Ref.**
1	CXB	Capsule	Either ethanol or acetonitrile	272 nm	0–3 mg/L	Ethanol = 0.995 Acetonitrile = 0.999	29
2	CXB	Capsule	Methanol	270 nm	10 to 50 µg/ml	0.9965	30
3	CXB	In pure form and in solid dosage form	High pure water, methanol, acetonitrile	251 nm	1–20 µg/ml	0.9999	31
4	AMD and CXB	harmacuetical Formulation	Ethanaol	364.3nm and 286.7nm	0.5 to 10 μg/ml and 5 to 40 μg/ml	0.9992 and 0.9990	32
5	CXB and AMD	Tablets	Methanol	250 nm And 290 nm	40 μg/ml and 3–8 μg/ml	0.9992 and 0.9991	33
6	AMD, CXB and RMP	Pharmaceutical combined dosage forms	Methanol	361 nm, 253nm and 222 nm	5–60 µg/ml, 5–30 µg/ml, and 5–110 µg/ml	0.9998, 0.9998 and 1	34
7	AMD and CXB	Pure and pharmaceutical Formulation	Ethanol	334.2 nm and 254.2 nm	1–6 µg/ml and 5–40 µg/ml	0.9994 and 0.9999	35
8	AMD and CXB	Pure and combined dosage form	Methanol	237nm and 252nm	2 to 12µg/ml	0.9981 and 0.9984	36

*** Not Provided

Liquid-Chromatography-Mass Spectroscopy methods (LC-MS) for CXB:

In recent years, the combination of LC/MS has gained a lot of attention for the analysis of interest analytes in complex samples with improved performance. In brief, after a thorough examination, LC/MS interfaces are divided into two categories namely interfaces for indirect and direct input of column effluent. A mechanical mechanism is employed to transmit the column effluent to the MS vacuum at an indirect introduction interface. A classic example of an indirect introduction type of interface is the transportation system. In the case of the direct introduction system, the column effluent flows directly into the mass spectrometric vacuum system via a tube. Mainly, the most straightforward method of linking LC and MS appears to be the direct introduction.33 In this section, we have discussed the LC-MS methods for the determination of CXB in a dosage form **Table 3**.

Table 3. Summary of LC-MS methods for the determination of CXB in a dosage form

Sr. No	Drug	Matrix	ationary Phase	Mobile Phase	Internal Standard	Linearity (ng/mL)	Ref.
1	CXB	***	Symmetry C18 analytical column	5.0 mm ammonium acetate- acetonitrile in the ratio of 30:70 (v/v)	***	0.06 to 3.0 ppm	37
2	CXB	Bulk and formulation s using a chiral column	Chiralcel OD column	Hexane: Ethanol (94:06 v:v)	***	0.25–0.75 mg:ml	38

*** Not Provided

HPLC method for CXB

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high. The summary of the reported HPLC methods is shown in **Table 4.**

Table 4: Summary of HPLC methods for the determination of CXB in a single and combined dosage form

Sr. No.	Drug name	Column	Mobile phase	Lambda max(nm)	Linearity (µg/mL)	ntion time (min)	Flow rate (mL/min)	Detector	Ref.
1	CXB	tsil ODS-3 column	etonitrile:water (55:45 v/v)	242 nm	0.25 to 1.0 g/ml	16.55 min	1.0 ml/min	SPD-M10AVP photodiode array detector	39
2	CXB	Column L11	Buffer, Methanol and Acetonitrile (60: 30: 10v/v/v)	215nm	25-120 g/ml	23.501 min	1.3 ml/min	VWD detector	40
3	CXB	Reversed- phase C-18 column	Buffer and acetonitrile (40:60)	254 nm	to 150 mg/ml	10.9 min	1 ml/min	o-diode array detector	41
4	CXB	Reversed- phase C-18 column	Methanol and water (85:15)	251 nm	2 to 50 mg/ml	4.965 min	0.8 ml/min	Ultraviolet (UV)-visible detector	42
5	CXB	Reversed- ase C-18 column	Methanol and (75:25 % v/v)	250 nm	0.27–80 µg/ml	4.8 ± 0.01 min	1.25 ml/min	UV–visible detector	43
6	AMD and CXB	Zorbax C18	Sodium phosphate buffer (ph 5.6) : acetonitrile :	239 nm	5–30 µg/ml and 50–500 µg/ml	1.72±0.02 min 3.38±0.023 min	1.2 ml/min	UV detector	44

			methanol in a ratio 30:55:15 (v/v)						
7	CUR and CXB	RP C18 XDB column	Water (1% acetic acid)- Acetonitrile	254 nm	1- 20 µg/ml and 0.1-2 µg/ml	***	1.50 ml/min	UV/Vis detector	45
8	AMD and CXB	C18 reversed phase column (Thermo ODS Hypersil	Acetonitrile: potassium phosphate Buffer 60:40 (v/v)	360 nm d 265 nm	0.017 and 0.0167 µg/ml	4.41min and 7.30 min	1 ml/min	UV detector	46
9	AMD and CXB	Reversed- phase C-18 column	EOH + Water (70:30 v/v)	235 nm	1-5 µg/ml and 20-100 µg/ml	3.953 min and 6.587 min.	1 ml/min	UV Detector	47
10	ATV-Ca and CXB	mosil-C18 column	Acetonitrile: ammonium acetate buffer: methanol (50:25:25 v/v/v)	277nm	100-500µg/ml	195 min and 3.989min	1.0ml/min	UV/Vis detector	48
11	CXB and AMD	masil C18 column	Methanol and potassium dihydrogen phosphate 70:30% v/v	253 nm	10-60 µg/ml and 1-6 µg/ml	2.89 min and 5.89 min	1.2 ml/min	UV Detector	49
12	CXB and DIN	Inertsil ODS 3V L1 column	Methanol and acetonitrile; 50 : 50, v/v	255 nm	10-40 µg/ml and 5-20 µg/ml	7.42 min and 13.96 min	1.0ml/min	odiode array detector	50
13	AMD and CXB	Florosil C18 analytical column	Acetonitrile-Water (80:20 v/v)	250 nm	2-12 µg/ml and 50-300 µg/ml	1.98 min and 3.18 min	1.0ml/min	UV/Vis detector	51

HPTLC method for CXB

Thin-layer chromatography is a popular technique for the analysis of a wide variety of organic and inorganic materials, because of its distinctive advantages such as minimal sample clean- up, a wide choice of mobile phases, flexibility in sample distinction, high sample loading capacity and low cost. The summary of the reported HPTLC methods is shown in **Table 5.**

Table 5: Summary of HPTLC methods for the determination of CXB in a single and combined dosage form

Sr. No.	Drug	Stationary Phase	Mobile Phase	ection	Linearity	Ref.
1	CXB	Silica gel 60F254	N-hexane–ethyl acetate, 60 + 40 (v/v)	262 nm	200 and 2000 ng/spot	52
2	AMD and CXB	Pre-coated silica gel aluminium Plate 60 F254	Toluene : ammonia : methanol : acetonitrile (6.6:0.12:1.5:2 v/v/v/v)	240 nm	0.3-2 µg/spot 0.3-3.4 µg/spot	53

Conclusion

The current review article offers a thorough understanding of the many analytical and bioanalytical techniques both singular and combined developed for celecoxib. Numerous novel analytical techniques, including as UV spectroscopy, UPLC, HPLC, and HPTLC, have been published for analysis purposes. The method has been tabulated and includes information regarding the mobile phase, stationary phase, retention time, etc. for the researchers' convenience. Future analytical techniques for the bio-analysis of celecoxib in pharmacological and biological formulations can be developed using the information acquired. In conclusion, it offers an opportunity to gain additional insight into past achievements and prospective future initiatives and modifications aimed at expanding our understanding of celecoxib.

Conflict of interest

The authors declare that no conflict of interest

Abbreviations

1. UV/VIS – Ultra violet/visible spectroscopy
2. HPLC – High-performance liquid chromatography
3. HPTLC – High-performance thin layer chromatography
4. LC-MS/MS – Liquid chromatography-mass spectroscopy-mass spectroscopy
5. UPLC – Ultra performance liquid chromatograpy
6. RP – Reverse phase
7. nm – Nanometer
8. µg/mL – Micro gram per Milliliter
9. PDA - Photo diode array
10. CXB – Celecoxib
11. ETX – Etoricoxib
12. VDX – Valdecoxib
13. PRX – Parecoxib
14. RFX – Rofecoxib
15. LMX – Lamiracoxib
16. REP – Repaglinide
17. DTX – Docetaxel
18. IBU – Ibuprofen
19. DIC – Diclofenac
20. NIF – Niflumic Acid
21. OH-CXB – Hydroxycelecoxib
22. COOH-CXB – Carboxycelecoxib
23. SCA – Salicylic acid
24. KPF – Ketoprofen

25. NMS – Nimesulide
26. DEZ – Dezocine
27. DEX – Dexmedetomidine
28. AMD – Amlodipine

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